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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/871,339	MADIYALAKAN ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1, 2, 4, 7-10 and 16-29 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 3, 5, 6, 11 and 12 have been canceled. Claims 1, 2, 4, 7-10 and 16 have been amended. Claims 17-29 have been added. Claims 1, 2, 4, 7-10 and 16-29 are pending and under consideration.

2. Text of sections of Title 35, U.S. Code not found in this action, can be found in a previous action.

3. With regard to applicant's contention that the examiner used references after the claimed priority date, applicant is directed to the M.P.E.P. (2124) wherein it is stated:

> 2124 Exception to the Rule That the Critical Reference Date Must Precede the Filing Date
> IN SOME CIRCUMSTANCES A FACTUAL REFERENCE NEED NOT ANTEDATE THE FILING DATE
> In certain circumstances, references cited to show a universal fact need not be available as prior art before applicant's filing date. In re Wilson, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). Such facts include the characteristics and properties of a material or a scientific truism.

In the instant case, the references were clearly used to provide evidence of the properties of the antibody.

4. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 recites "antibody...presents one or more epitopes on the antigen other than the first epitope". It is unclear what the epitope is being presented to. The art recognizes that MHC I and II "present" T-cell epitopes to T cell receptors. The meaning of "present" as used in the instant claim is not clear in reference to the action of an antibody

5. Claims 1, 2, 4, 7-10 and 16-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to a circulating tumor-associated antigen

Claims 1, 4, 10, 16 have been amended to recite "circulating tumor antigen". New claims 21, 22, 23 and 29, also contain the embodiment of "circulating" tumor antigen. The originally filed disclosure described "soluble" tumor antigens which were shed into the bloodstream as opposed to a surface antigen (page 18, lines 7-12). The amendment to "circulating" tumor antigen is broader in scope than the originally disclosed "soluble" tumor antigen because "circulating" tumor antigens would include tumor antigens on cells which were "circulating" versus "shed" tumor antigens, and the cell-surface associated type of tumor antigen was excluded by the specifications definition of soluble tumor antigen (page 18, lines 7-12).

(B) As drawn to the Sialyl Lewis A, Sialyl Lewis X, prostate specific antigen, carcinoembryonic antigen and CA50.

Claims 23 and 29 require the tumor antigens of sialyl-LeA, sialyl-LeX, PSA, CEA and CA50. None of these antigens were described in the originally filed disclosure.

Applicant states that the specification incorporates by reference U.S. 5,075,218 and U.S. 4,471,07 at pages 18, line 6 and page 19, lines 24-27. After reviewing the textual reference, it was determined that the above patents were merely cited but were not incorporated by reference in the original specification. The M.P.E.P. (608.01(p)) states

> Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973).

Thus, one of skill in the art would reasonably conclude that applicant was not in possession of the claimed invention.

6. Claims 1, 2, 4, 7-10 and 16-29 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting growth of cancer cells and eliciting a therapeutic immune response in a patient comprising administering a non-radiolabeled B43.13

antibody which specifically binds to a soluble CA125 antigen within said patient and therapeutic compositions comprising non-radiolabeled antibodies, does not reasonably provide enablement for a method of inhibiting growth of cancer cells and eliciting a therapeutic immune response in a patient comprising administering a non-radiolabeled antibody which binds to a first epitope on the tumor associated antigen and elicits and effective immune response against a second epitope on the tumor antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

The instant specification contemplates that a tumor associated antigen may possibly undergo an alteration in conformation (page 21, lines 7-15)

"The binding agents of the present invention bind the multi-epitopic tumor antigen of interest, and the resulting immunogenic pair may be used to prime or initiate an immune response to another epitope on the antigen. As noted in more detail elsewhere in this disclosure, it is believed that the binding event between the binding agent and the multi-epitopic antigen changes the conformation of the antigen sufficiently to provide access to another previously unrecognizable epitope on the antigen. The previously unrecognizable epitope, once recognized by agents of the immune system, initiates the immune system cascade that results in an immune response to the whole antigen.".

The specification fails to teach characteristics of the first epitope of the tumor associated antigen relative to the second epitope of the tumor antigen, or the location of the antibody complex of the tumor associated antigen which would cause the re-conforming of the tumor associated antigen and recognition of the second epitope necessary to expose a previously unrecognizable epitope on said antigen so that one of skill in the art could reliably elicit this effect given any tumor antigen. Protein-protein interactions are complex in nature and the teachings of the art cannot be relied upon for a nexus between the binding of an antibody to an epitope on a tumor associated antigen and the change in conformation of the antigen-antibody pair necessary for the exposure of a previously unrecognized epitope. The art (Colman, Advances in Immunology, 1988, Vol. 43, pp. 99-132, cited in a previous Office action) teaches that antigens which are bound by an antibody can exhibit no conformational change (page 123, lines 1-3 under the heading "Antigen"), small conformational changes (page 123, lines 7-27 under the heading "Antigen") or much larger structural changes (page 124, lines 3-6). Thus, given the teachings of Colman, one of skill in the art would ascertain that there is no guarantee

that the binding of an antibody to an antigen will produce any conformational change, or enough of a conformational change to expose a previously hidden epitope. Neither the art nor the specification provide teachings as to the nexus between the binding of an antibody to an antigen and a resulting conformational change in said antigen that would expose an epitope which was not recognized in the unbound antigen.

The specification describes B43.13 as an antibody which binds to the ovarian cancer antigen 125 at the B43.13 epitope. The specification states "Once the B43.13 antibody binds to the CA 125 antigen, either the conformation of the antigen is altered or the antigen is processed and/or delivered differently so that it is recognized by the host's immune system" (page 17, lines 5-8). The specification fails to provide actual teachings that the reconfirming of the CA 125 antigen actually took place. The specification fails to teach how to recognize other epitopes which would result in the "re-conforming" of the tumor antigen upon binding of the "binding agent" or antibody. The specification fails to teach criteria for the "binding agent" which would result in a re-conforming of the tumor antigen after binding. The art teaches that the presence of an antibody antigen complex is recognized by the immune system in a different way than the presence of the antigen alone. Thus, the art supports the assertion of the specification that "the antigen is processed or delivered differently" so that it is recognized by the host's immune system, rather than the altered conformation of the CA 125 antigen eliciting the host immune response. Given that the specification fails to provide data supporting the notion that the CA 125 antigen bound by the B43.13 antibody produced an altered conformation of the CA125 antigen which is responsible for the induction of the host immune response, and the lack of teachings in the specification regarding the structural requirements of both the tumor associated antigen and the binding agent which would produce said altered conformation of the tumor associated antigen, and the teachings of the art which indicate that altered conformation of an antigen upon binding of an antibody is unreliable, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the claimed invention.

Simitsek et al (cited in a previous action) teach that the processing of T-cell determinants can be modulated by the presence of a bound antibody, and that a high affinity antibody which remains tightly bound to the antigen at the acidic pH of endosomes can inhibit protease

accessibility by antibody protection (page 1962, first column, lines 11-16). Simitsek et al teach that other determinants which are physically separated from the antibody have an increased likelihood of being captured for class II MHC presentation relative to the determinant that is directly bound by the antibody (page 1962, bridging paragraph and second column, lines 16-20). However, the teaching of Simitsek et al do not enable the instant method claims because there is no direction for how to guarantee the selection of an alternative epitope. There is no teaching regarding the physical constraints necessary to alter the presentation of antigen in the context of MHC given that every multi-epitopic tumor antigen has immunogenic epitopes which exist at completely variant intervals, and therefore one of skill in the art would need to know how far the steric constraint of the antibody has any effect. Further there is no teachings in the specification regarding how to determine immune response elicited against the second, undescribed epitope will be efficacious.

It is noted that the same rejection was applied to claim 12 which is now canceled. However, claims 1, 10 and 16 have been amended to re-incorporate the same subject matter.

7. Claims 1, 2, 4, 8, 10, 16-24 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al (Biotechnology Therapeutics, 1992, Vol. 3, pp. 81-89, reference B8 of the IDS filed August 8, 2001) and Madiyalakan et al (Hybridoma, 1995, Vol. 14, pp. 199-203, reference of the IDS filed August 6, 2001).

Claim 1 is drawn to a method for inhibiting growth of cancer cells comprising administering a composition comprising a non-radioactive antibody that specifically binds to a first epitope on a circulating tumor associated antigen thereby generating an immune response against a second epitope on the tumor associated antigen and eliciting a host immune response against cancer cells producing the antigen.. Claim 2 embodies the method of claim 1 wherein the antibody is selected from the group consisting of a monoclonal, chimeric, humanized, genetically engineered monoclonal, Fab, F(ab')2 and a single chain antibody. Claim 4 embodies the method of claim 2 wherein the circulating tumor associated antigen is selected from the group consisting of CA 19.9, CA 15.3 and CA 125. Claim 8 embodies the method of claim 1 wherein the host immune response is a humoral immune response

Claim 10 is drawn to a method for eliciting an immune response in a host comprising administering to the host a composition comprising an non-radiolabeled antibody that specifically binds to a first epitope on a circulating tumor associated antigen thereby generating a therapeutic host immune response against a second epitope on the antigen. Claim 19 embodies the method of any one of claims 1-2, 4 and 7-10, wherein the composition further comprises one or more adjuvants, one or more carriers, one or more excipients, one or more stabilizers, one or more imaging reagents, one or more pharmaceutically acceptable carriers and/or physiologically acceptable saline. Claim 20 embodies the method of any one of claims 1-2, 4 and 7-10, wherein the composition is administered by any acceptable route selected from the group consisting of intravenous, sub-cutaneous, intradermal, intramuscular and intralymphatic injection. Claim 21 embodies the method of any one of claims 1-2, 4 and 7-10, wherein the circulating tumor-associated antigen is a soluble antigen. Claim 22 embodies the method of any one of claims 1-2, 4 and 7-10, wherein the binding of the antibody to the first epitope on the circulating tumor-associated antigen presents one or more epitopes on the antigen other than the first epitope.

Madiyalakan et al (Hybridoma, 1995, Vol. 14, pp. 199-203) teach that a statistically significant number of patients who survived for more than 2 years had induction of the anti-idiotype network as evidence by the presence of Ab2 (page 202, second column, lines 54-59). Madiyalakan et al teach that the development of the Ab2 antibodies correlated with the presence of circulating antigen in the patients (page 203, lines 6-10).

Wagner et al teach a method of treating cancer, a method of eliciting an immune response against CA 125, and a method of increasing immunogenicity of CA125 comprising administering to ovarian cancer patients F(ab)2 fragments of OC125 mAb which is radiolabeled. (page 83, under the heading "Patients and Methods"). Wagner et al teach that the survival rates for patients who developed anti-idiotypic antibodies was greater than the survival of patients being treated with chemotherapy and surgery (Figure 3). Thus, the disclosure of Wagner fulfills the specific embodiments of claims 1, 10 and 11 drawn to a method of treating cancer, a method of eliciting a therapeutic immune response and a method for increasing the immunogenicity of an antigen, because the administration of the CA125 mAb caused increased survival in cancer patents and evoked a host immune response. Further the limitation of claim 8 drawn to a humoral immune response is met by the induction of the anti-idiotypic response. It is noted that

Wagner et al administered the radiolabeled F(ab)2 fragments for diagnostic purposes. However, Wagner et al state that "We do not assume that the infused radiolabeled antibody fragments, having a total amount of radioactivity of less than 3 mCi could be responsible for the therapeutic effects, since the given dose was at least 40 times lower than that which is normally applied for targeted radiotherapy" (page 86, line 13 to page 87, line 3). Wagner et al suggest that the induction of the anti-idiotypic network was responsible for the observed therapeutic effects (abstract).

It would have been prima facie obvious at the time the claimed invention was made to administer non-radiolabeled B43.13 antibodies to patients having soluble CA125 levels in their blood. One of skill in the art would have been motivated to do so by the teachings of Madiyalakan et al on the correlation between levels of CA125 in the blood, the induction of the anti-idiotypic network as evidenced by Ab2 and the prolonged survival of said patients, in addition to the teachings of Wagner et al who suggest that the induction of the anti-idiotypic network was responsible for the effects seen with the radiolabeled B43.13 antibody which did not have enough specific activity to account for the direct killing of tumor cells by radioactivity. One of skill in the art would understand that it is not necessary to have a radiolabeled antibody to induce the anti-idiotype network, because the anti-idiotype network relies upon the production of a secondary antibody which binds to the idiotype of the first antibody, etc, and there is nothing in the art suggesting the requirement for a radiolabeled antibody for this induction as the first antibody serves as the antigen for the production of the second antibody, and it is well known in the art that an antigen need not be radiolabeled to induce an immune response.

8. The rejection of claims 1, 2, 4, 7-10 and 16 under 35 U.S.C. 103(a) as being unpatentable over Chang et al (EP 153,871) in view of Simitsek et al (Journal of Experimental Medicine, 1995, Vol. 181, pp. 1957-1963) and the abstract of Golumbek et al (Immunologic Research, 1993, Vol. 12, pp. 183-192) and Jacobs et al (Current Problems in Cancer, 1991, pp. 299-350) is maintained for reasons of record. New claims 17-24 and 29 are also rejected for the same reasons of record..

The specific embodiments of claims 1, 2 and 7-10 are set forth above. Claim 4 embodies the method of claim 2 wherein the multi-epitopic tumor associated antigen is CA 19.9, CA15.3,

or CA125. Claim 16 is drawn to a therapeutic composition comprising a non-radiolabeled antibody specific for a first epitope on a circulating multi-epitopic in vivo tumor associated antigen, which antigen does not elicit an effective host immune response, wherein when the antibody present in the composition specifically binds a first epitope on the antigen and forms an antigen/antibody pair an effective host immune response is elicited against a second epitope on the antigen.

Chang et al (EP 153,871) teach a method of enhancing an immune response in vivo to an antigen comprising administering a complex of the antigen and a monoclonal antibody of the IgG1 or IgG2a class specific for the antigen, said complex formed with a molar excess of antibody, wherein the antigen is a tumor associated antigen or portion thereof, and an immunogenic composition comprising a complex of an antigen and a monoclonal IgG1 or IgG2 antibody specific for said antigen, wherein the antigen is a tumor associated antigen (claims 8, 9, 11 and 12). Chang et al teach that antigens complexed to antibody evoke a stronger immune response in T lymphocytes (page 7, lines 3-6). Chang et al teach that monoclonal IgG1 and IgG2a antibodies were superior to polyclonal human antibodies in evoking an immune response to hepatitis B antigen (page 11, lines 4-5) and that the enhancement of antigen-induced immune response of by monoclonal antibody was fund to occur with both soluble and particulate forms of antigen (page 11, lines 6-9). Chang et al teach that the Fc portion of the antibody is required for antibody potentiation of T lymphocyte proliferation (page 13, lines 14-15). Chang et al teach that antigen-antibody complexes can be used to produce antibody-secreting B lymphocyte clones through the augmentation of T-helper cells, which in turn expand the population of B cells that secrete antigen-specific antibody (page 14 line 30 to page 15, line 4). Chang et al teach that antigen-antibody complexes are especially useful for enhancing T cell response to antigens which are only marginally immunogenic (page 15, lines 12-15). Chang et al teach that antigen-antibody complexes for expansion of T-lymphocytes in vitro an be formed with IgG monoclonal antibody with an excess of antibody (page 16, lines 1-6 and lines 20-22). Chang et al teach that the preferred molar ratio of antigen to antibody ranges from about equivalence to about 1/100 (page 16, lines 26-28). Chang et al teach that antigen-antibody complexes can be formed with soluble antigens such as glucoproteins and that antigens of particular interest are tumor associated (page 17, lines 3-6). Chang et al do not specifically teach CA125, CA19.9 or CA15.3

as tumor associated antigens, or the induction of a host immune response against a second epitope on the tumor associated antigen versus which is not the epitope bound by the monoclonal antibody.

The abstract of Golumbek et al (Immunologic Research, 1993, Vol. 12, pp. 183-192) teach that the goal of immunotherapy is to break tolerance to tumor specific antigens.

Jacobs et al (Current Problems in Cancer, 1991, pp. 299-350) teach that the CA125 (page 327, lines 11-16 under the heading "CA 125"), CA19.9 (page 324, lines 13-15 under the heading "CA 19-9 and CA 50") and the CA15.3 (page 322, lines 10-13 under the heading "CA 15-3") antigens are tumor associated antigens present on the surface of cancer cells and shed into the blood of said cancer patients. Thus, the disclosure that CA 125, CA 19.9 and CA 15.3 as present in the serum fulfill the requirement of "circulating" antigen as set forth by Chang et al above.

It would have been prima facie obvious at the time the invention was made to administer mAb CA125, mAb CA19.9 or mAb CA15.3 complexed to their respective antigens to cancer patients, wherein the mAb was administered such that a slight excess of antibody in relation to antigen was attained in the blood of said patients. One of skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Chang et al on the use of antigen-antibody complexes containing a slight excess of antibody to expand antigen-specific t-lymphocytes in vivo; and the teachings of the abstract of Golumbek et al on the need for overcoming tolerance to tumor specific antigens.

Applicant argues that the abstract of Golumbek et al does not teach that the goal of immunotherapy is to break tolerance to tumor specific antigens because Golumbek et al teaches the genetic modification of tumor cells to express new antigens. This has been considered but not found persuasive. Applicant is directed to lines 1-4 of the abstract wherein it is stated that the goal of immunotherapy is to break tolerance to tumor antigens. The fact that Golumbek et al accomplishes this end by a different method does not teach away from the instant invention.

Applicant argues that there is no motivation to combine the teachings of Chang et al and Golubek and Jacobs because Golumbek and Jacobs teach self antigens and Chang et al teach foreign proteins. This has been considered but not found persuasive. Chang et al teach the general concept of how to T-cell response to antigens which are only marginally immunogenic.

There are no teachings in Chang et al which would cause one of skill in the art to limit the applicability of said teachings only to foreign proteins.

9. Claims 16, 17, 18 and 27-29 are rejected under 102(b) as being anticipated by either of Nudelman et al (U.S. 5,240,833) or Fagnani (EP 315,456).

Claim 16 is drawn to a therapeutic composition comprising a non-radiolabeled antibody specific for a first epitope on a circulating, multi-epitopic in vivo tumor associated antigen, which antigen does not elicit an effective host immune response, wherein when the antibody present in the composition specifically binds a first epitope on the antigen and forms an antibody/antigen pair and effective host immune response is elicited against a second epitope on the antigen. Claim 17 embodies the composition of claim 16 wherein the antibody is selected from the group consisting of a monoclonal antibody, a chimeric antibody, a humanized antibody, a genetically engineered monoclonal antibody, a Fab fragment, a F(ab')2 fragment and a single chain antibody. Claim 18 embodies the therapeutic composition of claim 16 further comprising one or more adjuvants, one or more carriers, one or more excipients, one or more stabilizers, one or more imaging agents, one or more pharmaceutically acceptable carriers and/or physiologically acceptable saline. Claim 19 embodies the therapeutic composition of claim 16 wherein the circulating multi-epitopic in vivo tumor associated antigen is selected from the group consisting of CA19.9, CA15.3, CA125, CA50, Sialyl-Lewis A, Sialyl Lewis X, PSA and CEA. Claim 27 embodies the therapeutic composition of claim 16 wherein the composition is formulated at a dose of about 2 mg/patient. Claim 28 embodies the therapeutic composition of claim 16 wherein the composition is formulated at a does of about 0.1 ug to about 200 ug per kg of body weight of a patient.

Nudelman et al disclose a therapeutic composition comprising the SNH3, NKH1, NHK2, NKH3 or NKH4 monoclonal antibodies and a physiologically acceptable diluents which include physiological saline (column 11, lines 5-11). Nudelman et al disclose that the pharmaceutically effective amount is from 1 to 5 ug per 100 grams body weight which is the same as 10 to 50 ug/kg body weight and about 2mg/pateint who weight about 150lbs. Nudelman et al disclose that the SNH3 monoclonal antibody binds primarily to sialyl Lewis-X; the NKH1, NKH2 NKH3

and NKH4 monoclonal antibodies binds to sialyl Lewis-A (column 8, line 33 to column 9, line 57).

Fagnani discloses a immunotherapeutic composition comprising an antibody or an antigen-binding fragment thereof which binds to CEA or PSA (page 30, claims 16 and 17, and page 3, lines 43-49) with a pharmaceutically acceptable diluent. Fagnani discloses a formulation in unit dosage form, each dosage containing 0.01 to 200 mg of an immunoglobulin conjugated to dextrans (page 9, line 54 to page 10, line 12) which meets the limitations of claims 27 and 28 when only the immunoglobulin portion of the conjugate is accounted for in terms of weight.

10. Claims 16, 17, 18 and 29 are rejected under 102(e) as being anticipated by either of Unger (U.S. 6,088,613) or Kokolus et al (U.S. 5,807,978).

Unger discloses a therapeutic composition comprising perfluorpentane vesicles comprising alkylated complexes of manganese as a magnetic resonance imaging agent which fulfills the specific embodiment of claim 18, and antibodies which bind to CA15-3 administered to a breast cancer patient (column 42, line 61 to column 43 line 1) which fulfills the specific embodiment of claim 29.

Kokolus et al disclose a therapeutic composition comprising an anti-PSA monoclonal antibody conjugated to a paramagnetic probes for in vivo detection which fulfills the specific embodiments of claims 18 and 29 (column 18, line 64 to column 19, line 3).

11. All other rejections and objections as set forth or maintained in the previous Office action are withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
5/16/2005

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER